

## TREATMENT OF SUPERFICIAL FUNGAL INFECTIONS OF SKIN AND NAILS

### SUMMARY

- + **Diagnosis should be confirmed by microscopy and culture, ideally before treatment is commenced.**
- + **Oral griseofulvin is the current treatment of choice for *T.capitis*.**
- + **Oral terbinafine is the treatment of choice for chronic dermatophyte infections.**
- + **“Pulse” itraconazole therapy is the treatment of choice for mixed dermatophyte and yeast infections in the nail or elsewhere.**

### INTRODUCTION

Superficial fungal infections affect millions of people throughout the world.<sup>1</sup> In Ireland, 10-12% on average, of a general practitioner's (GPs) consultations are skin related.<sup>2</sup> Superficial fungal infections characteristically involve the skin or nails with several organisms being responsible. Dermatophyte infections of the feet represent the most common fungal infections in developed countries due to the use of occlusive footwear.<sup>3</sup> The principle organisms involved belong to the genera *Trichophyton*, *Microsporum* and *Epidermophyton*. Yeast and mould infections complete the range.<sup>4,5,6</sup>

### TYPES OF FUNGAL INFECTION<sup>4,6,7,8</sup>

Tinea pedis	Also known as “athlete's foot,” it is the most common type of dermatophyte infection.
Onychomycosis	Fungal infection of the nails. It may be associated with chronic T.pedis infection.
Tinea cruris	Caused by dermatophyte or yeast organisms. Infection found in groin/genital region. Can be acquired from another infected area, most commonly the toe webs, on the same individual.
Tinea corporis	Usually affects the trunk, legs and arms. Characteristically, lesions are pink to red annular plaques, with scaly borders, which expand peripherally and clear centrally.
Tinea manuum	Dermatophyte infection of one or both hands - may be confused with chronic eczema.
Tinea capitis	Pre-pubertal children mainly affected. Early treatment is essential to prevent scarring alopecia. Examination and treatment of family members is important.
Pityriasis versicolor	Caused by <i>Malassezia furfur</i> . Frequently only noticed in the summer months when failure to tan occurs.
Candidiasis	Yeast infection found in intertriginous and mucocutaneous areas where heat and maceration provide a fertile environment.

### DIAGNOSIS

When a fungal infection is suspected, diagnosis should be confirmed by microscopy and culture of skin scales, plucked broken hairs or nail clippings.<sup>2,5,9-11</sup>

### TREATMENT

The choice of an anti-fungal agent is dependent on the site involved, the extent of clinical infection, the age and general health of the patient and concomitant drug therapy.<sup>4</sup> Superficial infections of the skin and nails may be managed either topically or systemically. Topical formulations are effective against localised infections but have limitations. They do not penetrate hair follicles,

thick keratin, or the nail plate effectively. Patients may find them inconvenient which may affect compliance.<sup>5,11,12</sup>

**Table 1: Treatments of Choice**<sup>4,6,9,15,16,18,20</sup>

ROUTE	CONDITION	DRUG TREATMENT
<b>Topical</b>	T.pedis, T.cruis, T.corporis, T.manuum	Imidazole e.g. miconazole BD or Terbinafine BD
	Pityriasis versicolor	Selenium sulphide 2.5% lotion
	Candidiasis	Imidazole BD or Polyene e.g. Nystatin BD / QDS
<b>Oral</b>	Onychomycosis	Terbinafine 250mg OD or “pulse” Itraconazole 200mg BD
	T.cruis, T.corporis	Terbinafine 250mg OD or Itraconazole 100mg OD
	T.capitis	Griseofulvin 500mg OD
	Pityriasis versicolor	Itraconazole 200mg OD
	Candidiasis	Itraconazole 100mg OD

Note: Duration of therapy may vary between conditions, refer to data sheet for details. All doses stated apply to adults.

### Azoles

Azole anti-fungals are available as both topical and systemic formulations. The imidazoles clotrimazole, econazole, miconazole, and sulconazole are available for topical application. These preparations may be sufficient for localised dermatophyte infections. Little difference in efficacy has been found between topical agents, so choice may be based on cost e.g. miconazole 2% being the least expensive.<sup>9</sup> These agents may be used to treat superficial fungal infections during pregnancy.<sup>19</sup> Tioconazole is a topical imidazole solution for local application to infected nails.

Itraconazole, ketoconazole, and fluconazole have all been investigated for the systemic treatment of superficial fungal infections of the skin and nails. Itraconazole, a substituted triazole anti-fungal, is active against both yeasts and dermatophytes. It is therefore useful for mixed infections that occur in the nail or elsewhere.<sup>20,21</sup> Usually given in a dose of 100-200mg daily, the duration of treatment is dependent on the site of infection. Itraconazole is effective for superficial fungal infections due to a “reservoir “ effect, where, because of its pharmacokinetics, it persists in skin, nails and hair follicles at therapeutic levels for some weeks.<sup>1,4,11,15</sup> This effect has made itraconazole particularly useful for onychomycosis. Therapy can be given as “pulse” rather than continuous treatment at a dose of 200mg twice a day for seven days. A twenty-one day tablet free period follows before another seven day treatment period. Two monthly cycles for fingernails and three monthly cycles for toenails are recommended.<sup>14,22-24</sup> Although studies failed to show superiority of “pulse” therapy over continuous, the dose for “pulse” therapy is half that of the continuous regimen, making “pulse” therapy a more cost effective option.<sup>22</sup> Maximum bioavailability of itraconazole is attained by taking it with or after food.<sup>4,20</sup> Itraconazole is not licensed for use in children under 16 years. Little experience of use in human pregnancy exists, however animal studies suggest a risk of fetal abnormalities, contra-indicating its use. Adequate contraceptive measures should be employed by women of child-bearing age during therapy and for one menstrual cycle after stopping therapy.<sup>15,20</sup> Small amounts of itraconazole are excreted into breast milk and

patients should avoid breast-feeding while taking itraconazole.<sup>20,25</sup> Ketoconazole, although effective, is no longer preferred for systemic treatment of superficial fungal infections due to rare cases of idiosyncratic and sometimes fatal hepatotoxicity.<sup>14</sup>

### **Terbinafine**

Available as a 1% cream or 250mg tablet, this fungicidal agent, active against dermatophytes, may only exert a fungistatic effect against certain *Candida* species.<sup>4</sup> High concentrations are found in the stratum corneum, hair and serum following systemic administration. It is the treatment of choice for onychomycosis with cure rates of 60-80% being reported.<sup>4,13,14</sup> Terbinafine is generally well tolerated with side effects usually noted within the first few weeks.<sup>15</sup> Redness and itching at the site of application have been reported with topical therapy. Adverse effects reported with systemic treatment include nausea, rashes, abdominal pain and rarely taste disturbances.<sup>4,16</sup> There is no clinical experience of use in pregnancy.<sup>23</sup> Terbinafine is excreted into breast milk and should be avoided in nursing mothers.<sup>16</sup>

### **Griseofulvin**

Isolated from *Penicillium griseofulvum* 40 years ago, the usefulness of this fungistatic agent is limited due to its narrow spectrum of activity.<sup>3,4,14</sup> It is effective against dermatophytes. Griseofulvin is licensed for use in children and is the current treatment of choice for *T. capitis*.<sup>17</sup> In onychomycosis, due to its low affinity for keratin, griseofulvin must be given for as long as the diseased nail is growing out e.g. for infected toenails duration of treatment is 12 to 24 months.<sup>4,14</sup> Relapse rates of 40% have been reported 3-12 months after the end of therapy, limiting its usefulness for this indication.<sup>5,14</sup> It is usually given in a dose of 500mg daily in adults and is best taken with food to facilitate absorption.<sup>5</sup> Griseofulvin is contra-indicated in pregnancy and women should not become pregnant during or within one month of treatment.<sup>25</sup> Due to damage of sperm cells by griseofulvin, males should not father children during treatment, or within six months of completion of treatment.<sup>18,25</sup> It is generally well tolerated with adverse effects including headache, GI disturbance and less commonly urticaria, diarrhoea and photosensitivity.<sup>5</sup>

### **Others**

Amorolfine is a morpholine derivative presented as a 5% nail lacquer solution for the treatment of onychomycosis.<sup>26</sup> Due to its special formulation, amorolfine requires once weekly application compared to tioconazole, which must be applied twice a day.<sup>11,26</sup> Its main disadvantage is that it requires the persistence and motivation of the patient e.g. filing the nail plate before application, for the full treatment period.<sup>11</sup> Amorolfine is therefore best reserved for patients when up to two nails are affected or for early nail plate infection.<sup>3,10</sup> Nystatin is a polyene antifungal available in a cream or ointment formulation for cutaneous candidiasis. It may be used as an alternative to an imidazole for topical treatment of candidiasis. Selenium sulphide is a non-specific anti-fungal agent effective in the treatment of pityriasis versicolor.<sup>12</sup>

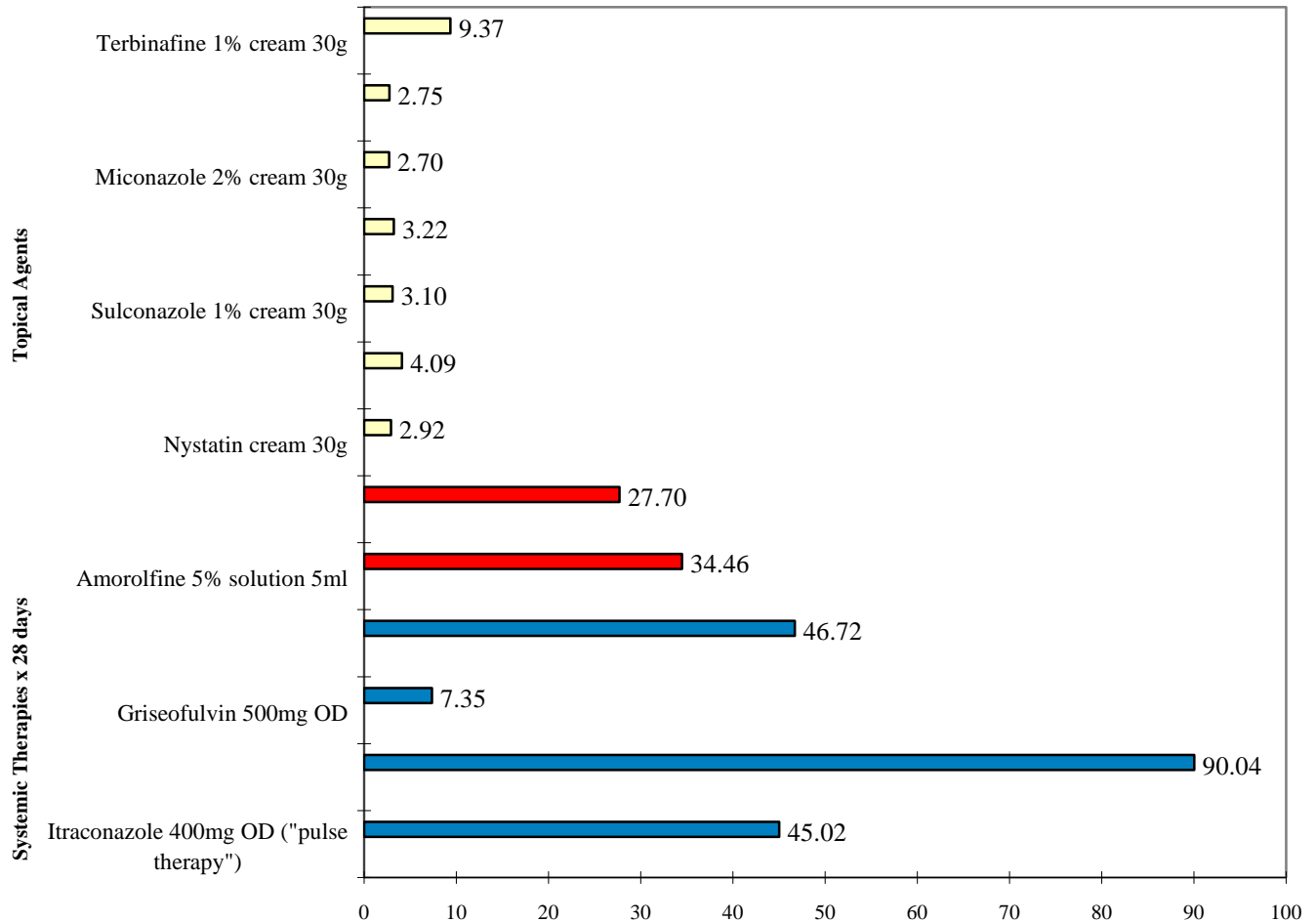
### **Drug Interactions**

No known drug interactions are thought to occur with terbinafine cream.<sup>16</sup> The potential for drug interactions with oral terbinafine therapy is less than that with azole anti-fungals. The metabolism of terbinafine, however, may still be affected by drugs that inhibit or induce the cytochrome p450 system, although the clinical significance of this is unknown.<sup>4,15,16,25,29</sup>

Griseofulvin is a potent inducer of cytochrome P-450 enzyme systems and several clinically significant drug interactions may occur. Griseofulvin is known to reduce the effects of anticoagulants and oral contraceptives ; patients should be informed and counselled appropriately. Information on griseofulvin enhancing the effects of alcohol and reducing the effects of phenobarbitone is limited.<sup>6,25,28</sup>

Itraconazole affects drugs that are metabolised via the cytochrome P-450 enzyme system. Dosage reductions may need to be undertaken in patients on itraconazole and warfarin or digoxin. The use of terfenadine, astemizole or cisapride with itraconazole is contra-indicated due to the risk of serious adverse effects e.g. cardiac toxicity and ventricular arrhythmias.<sup>11,20,25,29</sup> No clinically significant interactions have been reported with topical azoles.<sup>25,29</sup>

### Cost of Treatment (GMS/MIMS July 1998)



#### REFERENCES

- 1) Drugs 1996;52:209-224
- 2) IMN 1997: 17
- 3) J Am Acad Dermatol 1995;33:816-22
- 4) Prescriber 1998;9:43-75
- 5) Aust Prescr. 1996;19:72-75
- 6) Postgrad Med 1995; 98:61-75
- 7) Merck Research Laboratories "Merck Manual" 16<sup>th</sup> ed. 1992
- 8) J Am Acad Derm 1996;35:521-525
- 9) Leppard & Ashton. Treatment of Dermatology 1st ed. Radcliffe Medical Press Oxford, 1993
- 10) Practitioner 1997;241:745-749
- 11) J Am Acad Derm 1994;30:911-33
- 12) Br J Derm 1997;136:230-34
- 13) Arch Dermatol 1996;132:34-41
- 14) J Am Acad Dermatol 1997;36:231-5
- 15) BNF 1998 No.35:615
- 16) Ann P'cotherapy 1998;32:204-14
- 17) Lancet 1998;351:541-2
- 18) Product Info. Lamisil® 97/98

- 10) BMJ 1995;311:1277-81
- 11) MJA 1996;164:552-556
- 12) Am Fam Phys 1996;54:1687-1692
- 13) NMIC Bulletin 1997, Vol 3, No 3
- 14) Product Info. Sporanox® 97/98

- 24) DTB 1996;34:5-6
- 25) Product Info. Fulcin® 97/98
- 26) Product Info. Loceryl® 97/98
- 27) MJA 1996;165:274-279
- 28) Stockley I Drug Interactions. 4<sup>th</sup> ed. Pharmaceutical Press, London 1996.